Patterns of care and prognosis of older women with breast cancer

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Chapter 10

Summary and general discussion

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This thesis has three main conclusions:

1. There are large international differences in the treatment strategy of breast cancer among older women. These differences are not associated with a significant difference in prognosis.
2. The presence of comorbidity has an important impact on the general prognosis of older women with breast cancer. We did not show an important association between specific comorbidities or the use of co-medications and the breast cancer specific prognosis.
3. Concerning older women with breast cancer for research, there are very important methodological issues to take into account, including to avoidance of selection bias and the proper methodologies to take in to account the chance of dying from another cause of cancer: the competing risk of mortality.

THE FOCUS STUDY

A large part of this thesis is established using data from the FOCUS study. With the aim to develop guidelines for the treatment of older women with breast cancer, the FOCUS study was initiated in 2007: "Female breast cancer in the elderly: Optimizing Clinical guidelines USing clinico-pathological and molecular data". The FOCUS database is the largest, most detailed population-based database of older women with breast cancer. Worldwide, no other database of this size included only older women, and gathered this detailed data about the patients, tumour characteristics, treatment and follow up. In addition to clinical data, tumour tissues of a very large part of the included patients, was collected. The database consists of 3,672 consecutive breast cancer patients, aged 65 years or older at the time of diagnosis, diagnosed between 1997 and 2004 in the South West region of The Netherlands. In addition to the standard data included in the cancer registry, detailed information was gathered on the tumours' treatment and the occurrence of a recurrence during follow-up. Also, patient-related information was registered, including comorbidity and social economic status.

Within the FOCUS project, also large datasets from (national) cancer registries were shared for research projects. In addition, data from the TEAM trial were used. The Tamoxifen Exemestane Adjuvant Multinational was a large multicentre phase III trial on endocrine therapy. This is one of the few trials without an upper age limit, which results in a relative large number of older participants.

TREATMENT OF OLDER WOMEN WITH BREAST CANCER

The FOCUS study group has been conducting a number of studies in the available observational data and the relevant literature was reviewed. Important to note is that, due to the observational nature of the data that were used, it was impossible to directly link the observed treatment strategies in our cohorts to survival outcomes. This is due to the likelihood of introducing bias due to confounding by indication. In observational studies, treatment allocation is not controlled. Therefore, there can be several other factors related to treatment allocation, which interfere with the prognosis of a patient. This is one of the most important reasons why observational data should be interpreted with caution, especially when the intention of the study is to answer a prognostic question. One of the suggested methodologies to study treatment effects in observational studies, is using an Instrumental Variable.[1] This is a variable that is not directly related to the outcome, but which is related to the 'determinant'. In this thesis, two studies are included using country as an instrumental variable.

In **Chapter 2**, a large population-based study is discussed, using data from cancer registries from five European countries and the US (SEER database). In this study, local treatment as provided to older women with early breast cancer was compared between the countries. Large international differences were observed in the provision of *any* surgery, the type of surgery (breast conserving or mastectomy) and radiotherapy after breast conserving surgery. Despite these large differences, a rough comparison of survival data, showed no large international differences in survival. **Chapter 3** describes a follow-up study, in which all treatment modalities were assessed and compared between older women with breast cancer treated in Ireland and The Netherlands. This study also showed very large differences, in which the reluctance in local therapy seems to be compensated by providing more systemic (endocrine) therapy. Again, in this study, large treatment differences did not affect the outcome of the patients. These studies, in which treatment strategies are compared between countries, will be followed up by larger studies from the EURECCA group (EUropean REgistry of Cancer Care). In our opinion, these large population-based studies can provide us with a lot of knowledge. Especially for older patients, as stated before, there is a large gap in the literature, resulting in a lack of evidence for treatment. Probably, the answer to the questions that are still open for the treatment of older patients will not only come from randomized clinical trials, but also from observational studies, using proper methodology.

In **Chapter 4,** guideline adherence was shown to decline with increasing age at an international level. For this study, EUSOMA (European Society of Breast cancer specialists) provided their database, comprising data from 27 breast cancer units

across Europe associated to the society. In this study, the objective was to assess compliance to quality indicators, as defined by EUSOMA. The EUSOMA database consisted of 41.871 breast cancer patients across Europe. It was shown that among the oldest patients, aged 75 years and older, compliance to the indicators was significantly lowest, as compared to the younger age groups, with a tendency to *under* treatment. Interestingly, patients from the youngest age category (<40 years), were also observed to have a low compliance to the quality indicators. However, in this age group, there was an intention to *over* treatment.

COMORBIDITY AND CO-MEDICATIONS

An important early finding from the FOCUS studies is that cancer-specific prognosis of women with breast cancer declines with age, independent of tumour and treatment characteristics. This was studied both in the national cancer registry, as well as in the FOCUS cohort and the TEAM trial.[2-5] One of the possible explanations of the worse prognosis of older women with breast cancer is the impact of other diseases on prognosis, or the interaction of other diseases with breast cancer treatment. Therefore, in **Chapter 5** of this thesis, the FOCUS database was used to study if the existence of comorbidity during diagnosis was associated with the breast cancer specific prognosis. It was demonstrated that the number of comorbidities, but also a number of specific diseases by itself were associated with a higher overall mortality, which we considered as an expected result. More interestingly, it was found that more comorbidity was associated with a higher recurrence risk among younger elderly (<75 years), but with a *lower* recurrence risk among the oldest elderly (75 years and older). Also, the co-existence of psychiatric comorbidity (mostly reflecting dementia), was associated with a lower recurrence risk. New insights, which are discussed in **Chapter 9**, suggest this is the case of *competing mortality*: these women probably died from another cause than cancer, before experiencing a breast cancer recurrence. In **Chapter 6**, the association of the coexistence of diabetes during diagnosis and breast cancer prognosis among elderly was studied. In this study, a trend towards a more favourable cancer prognosis for diabetic women was observed, which was also most pronounced in the oldest patients. These findings are not thoroughly understood yet, but may **also** be explained by competing mortality: patients with more or severe comorbidity are at higher risk to die from another reason, before they can develop a cancer recurrence. Another possible explanation for the finding that breast cancer patients, with co-existing diabetes at the time of diagnosis, had a more favourable prognosis is the potential anti-cancer effect of metformin.[6] This hypothesis has been studied

in several observational studies; a clinical trial has also been designed to assess the association between the use of metformin and prognosis of breast cancer[7]. Results of this trial are not to be expected before 2023.

In **Chapter 7**, we present an observational study investigating the association of three different co-medications (including metformin, statins and beta blockers) and breast cancer specific prognosis. These analyses in postmenopausal hormone receptor positive early breast cancer patients, enrolled in the TEAM study, found less distant metastases in metformin, statin or beta blocker users, although not statistically significant. However, a statistically significant association between the use of statins and beta blockers and an improved breast cancer specific survival were demonstrated. These analyses are specifically important for the older patients. Conventional systemic adjuvant therapies, have shown to be associated with more adverse events and toxicity with increasing age. However, in our analyses no differences were observed between age groups, indicating that these drugs cannot serve as a specific new treatment option for breast cancer, neither in the elderly.

PROGNOSIS

One of the problems to face in the lack of evidence for treatment for older women with breast cancer, is the underrepresentation of elderly in clinical cancer trials.[8,9] Furthermore, in **Chapter 8,** we describe a study showing that older patients who are included in a large breast cancer trial, are not representative for the patients in de general population. In this study, patients from the population-based FOCUS cohort, who met the inclusion criteria for the TEAM study, were compared with the participants from the TEAM study aged 65 years and older. This study showed first, regarding patient characteristics, that women included in the trial had fewer comorbid diseases and a higher socioeconomic status. Moreover, although the same inclusion criteria were applied, tumours from women in the trial appeared to be smaller. Finally, the oldest patients (≥75 years) who participated in the trial, had a lower overall mortality than women from the population based cohort. The results of this study show that results from a clinical trial, can often not be extrapolated to the general population. The question is, if the current lack of evidence on the treatment of breast cancer among older women, can be filled with clinical trial results. Therefore, we suggest to use more observational study designs to fill the gap. Using the appropriate study designs, data obtained from observational studies can be of equivalent value as clinical trial results.[1] Probably, considering the older patients and their heterogeneity, which is an almost unsolvable issue in clinical trials, observational studies can be even more valuable.

In **Chapter 9**, we address one important issue to take into account using observational studies for prognostic research. In geriatric oncology, there are more goals to achieve than curing cancer, for instance, to preserve functional capabilities. Moreover, in older patients, the risk of competing mortality, i.e. dying of another cause than breast cancer, is a very important matter to take into account. The competing risk of mortality should be taken into account when making a treatment plan, but also in research. In this chapter, we show with an example study, using data from the FOCUS cohort, that not using the appropriate model in risk prediction in a population with a high risk on competing mortality, can result in an overestimation of the real risk on cancer-specific events. Therefore, when predicting the prognosis in a population with a high risk of competing mortality, we advise to use specific models taking into account this risk of competing mortality, to make a more adequate estimation of the risk of interest. This risk of competing mortality should also be taken into account when making decisions about treatment. In clinical practice, this is a process taking place in the physician's room, or in the multidisciplinary team, when the treatment plan is being discussed. Currently, physicians are forced to determine this risk by their 'gut feeling', to decide how aggressive or reluctant the patient sitting in front of them will be treated.

FUTURE PERSPECTIVES

Recently it was shown, that the most frequently used and recommended tool, 'Adjuvant! Online' is not able to accurately predict the prognosis of breast cancer patients aged 65 years or older. Using data from the FOCUS cohort, the actual prognosis was compared with the predicted prognosis by Adjuvant! Online. Using the tool, overall survival appeared to be *over*-estimated by 9.8%. This overestimation was even larger in patients aged 75-79 and 80-84, compared to younger elderly. Also, the degree of overestimation increased with increasing numbers of comorbidities. These findings can probably be explained by the fact that the Adjuvant! Online model is created using a cohort from which elderly patients were excluded: there was an upper age limit of 69 years.[10] Therefore, this study implies that results derived from younger (and obviously healthier) patients, cannot be extrapolated directly to an older population of patients with the same disease.

Another, increasingly used prediction tool is the PREDICT tool. This tool was also subject to a validation study, using the FOCUS data. In this validation study, the PREDICT tool was shown to be more accurate in the prediction of the prognosis of older patients, compared to the previously described Adjuvant! Online tool.[11] The most reasonable explanation for the more accurate prediction is that de PREDICT

tool was designed in a cohort including a relatively large number of older women. Also, PREDICT added two extra markers to the model: HER-2 and Ki-67.

The available tools, have one thing in common: they predict the prognosis in terms of recurrence free survival or overall survival. Currently, the FOCUS study group is working on new studies among older women with breast cancer. In this novel study, a prediction model will be created using the data from the FOCUS cohort. In this model more patient characteristics will be added to the formerly used, conventional predictors. Suggested endpoints are: overall survival, treatment toxicity, quality of life and functional decline.

The studies described in this thesis, along with the other studies performed by the FOCUS study group, have highlighted the urgent need for a new type of investigation to create a tool which might assist in identifying the individualised treatment strategy for older women with breast cancer. This will have to take into consideration patient's *and* the tumour's information as well as the endpoints for each individual patient.

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